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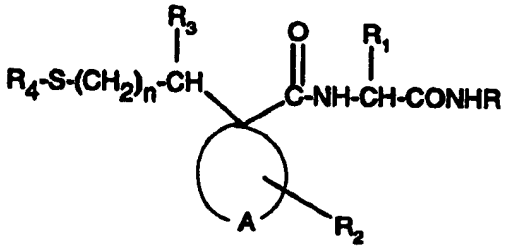
(54) Title: CERTAIN CYCLIC THIO SUBSTITUTED ACYLAMINOACID AMIDE DERIVATIVES

(57) Abstract

Disclosed are compounds of formula (I), wherein R, R_1, R_2, R_3, R_4, A and n are as defined; pharmaceutically acceptable salts thereof; disulfides corresponding to said compounds of formula (I) wherein R_4 is hydrogen; methods for preparation thereof; pharmaceutical compositions comprising said compounds; and a method of inhibiting TNF–alpha and matrix–degrading metalloproteinase activity and of treating TNF–alpha and matrix metalloproteinase dependent diseases or conditions, e.g. inflammatory conditions, osteoarthritis, rheumatoid arthritis and tumours, in mammals using such compounds.



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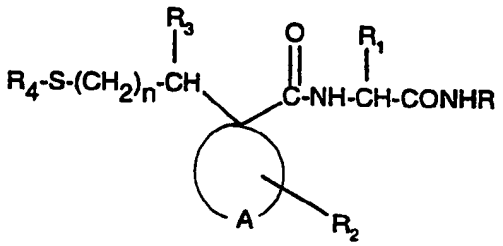
CERTAIN CYCLIC THIO SUBSTITUTED ACYLAMINOACID AMIDE DERIVATIVES

The present invention relates to novel thio substituted cyclic acylaminoacid amide derivatives described below, as inhibitors of matrix-degrading metalloproteinases and TNF alpha (tissue necrosis factor alpha) activity, methods for preparation thereof, pharmaceutical compositions comprising said compounds, a method of inhibiting TNF alpha and matrix degrading metalloproteinase activity and a method of treating TNF alpha and matrix metalloproteinase dependent diseases or conditions in mammals which are responsive to matrix metalloprotease and TNF alpha inhibition, using such compounds or pharmaceutical compositions comprising such compounds of the invention.

The present invention relates to the cyclic thio substituted acylaminoacid amide derivatives of formula I



(I)

wherein

R represents hydrogen, lower alkyl, cycloalkyl, bicycloalkyl, adamantyl, aryl, biaryl, or mono- or di-(cycloalkyl, aryl or biaryl)-lower alkyl, di-(lower alkyl or aryl-lower alkyl)-amino-lower alkyl, or (piperidino, morpholino, pyrrolidino)-lower alkyl;

R_1 represents hydrogen, lower alkyl, cycloalkyl, aryl, biaryl, or (cycloalkyl, aryl or biaryl) - lower alkyl;

R_2 represents hydrogen, lower alkyl, lower alkoxy, aryl-lower alkyl, aryl-lower alkoxy, amino, mono- or di-(lower alkyl or aryl-lower alkyl)-amino, acylamino, or (lower alkyl or aryl-lower alkyl)-(thio, sulfinyl or sulfonyl);

R_3 represents hydrogen, lower alkyl, cycloalkyl, aryl-lower alkyl, cycloalkyl-lower alkyl, or C_2-C_7-alkyl interrupted by S, SO, SO_2, O or N-R_5;

R_4 represents hydrogen or acyl;

R_5 represents hydrogen, lower alkyl, aryl-lower alkyl, acyl, or (lower alkyl, aryl or aryl-lower alkyl)-sulfonyl;

A together with the carbon to which it is attached forms a ring and represents a bivalent radical of the formula $(CH_2)_P$ which may be interrupted by S, SO, SO_2, O, or N-R_5;

n represents an integer from zero to four;

p represents an integer from 2 to 6;

any pharmaceutically acceptable salts thereof;

and disulfides corresponding to said compounds of formula I wherein R_4 is hydrogen.

The compounds of the invention depending on the nature of the substituents, possess one or more asymmetric carbon atoms. Also the A-containing ring substituent R_2 is either cis or trans to the amide grouping. The resulting diastereoisomers, enantiomers and geometric isomers are encompassed by the instant invention.

Preferred are the compounds of the invention wherein the configuration of the asymmetric carbon atom of the terminal amino acid amide moiety corresponds to that of an L-amino acid precursor and is assigned the (S)-configuration.

Further preferred are the compounds of formula I in which the A-containing ring is e.g. cyclohexane in which the substituent R_2 is at the 4-position and is preferably cis to the amide grouping.

Compounds in which R_4 is acyl represent prodrug acyl derivatives and are preferably those derived from an organic carbonic acid, an organic carboxylic acid or a carbamic acid.

An acyl derivative which is derived from an organic carboxylic acid is, for example, lower alkanoyl, phenyl-lower alkanoyl or unsubstituted or substituted aroyl, such as benzoyl.

An acyl derivative which is derived from an organic carbonic acid is, for example, alkoxycarbonyl, especially lower alkoxycarbonyl, which is unsubstituted or substituted by carbocyclic or heterocyclic aryl or is cycloalkoxycarbonyl, especially C_3-C_7-cycloalkyloxycarbonyl, which is unsubstituted or substituted by lower alkyl.

An acyl derivative which is derived from a carbamic acid is, for example, aminocarbonyl which is substituted by lower alkyl, carbocyclic or heterocyclic aryl-lower alkyl, carbocyclic or heterocyclic aryl, lower alkylene or lower alkylene interrupted by O or S.

Pharmaceutically acceptable salts of any acidic compounds of the invention are salts formed with bases, namely cationic salts such as alkali and alkaline earth metal salts, such as sodium, lithium, potassium, calcium, magnesium, as well as ammonium salts, such as ammonium, trimethylammonium, diethylammonium, and tris-(hydroxymethyl)-methylammonium salts.

Similarly acid addition salts, such as of mineral acids, organic carboxylic, and organic sulfonic acids e.g. hydrochloric acid, methanesulfonic acid, maleic acid, are possible provided a basic group, such as pyridyl, constitutes part of the structure.

The general definitions used herein have the following meaning within the scope of the present invention, unless otherwise specified.

The term "lower" referred to above and hereinafter in connection with organic radicals or compounds respectively defines such as branched or unbranched with up to and including 7, preferably up to and including 4 and advantageously one or two carbon atoms.

A lower alkyl group is branched or unbranched and contains 1 to 7 carbon atoms, preferably 1-4 carbon atoms, and represents for example methyl, ethyl, propyl, butyl, isopropyl or isobutyl. Lower alkyl for R_1 is preferably C_2-C_5-alkyl, advantageously C_2-C_4-alkyl.

Lower alkylene in general represents either straight chain or branched alkylene of 1 to 7 carbon atoms and represents preferably straight chain alkylene of 1 to 4 carbon atoms, e.g. a

methylene, ethylene, propylene or butylene chain, or said methylene, ethylene, propylene or butylene chain mono-substituted by C_1-C_3-alkyl (advantageously methyl) or disubstituted on the same or different carbon atoms by C_1-C_3-alkyl (advantageously methyl), the total number of carbon atoms being up to and including 7.

Lower alkylenedioxy is preferably ethylenedioxy or methylenedioxy.

Esterified carboxyl is for example lower alkoxycarbonyl or benzyloxycarbonyl.

Amidated carboxyl is for example aminocarbonyl, mono- or di-lower alkylaminocarbonyl.

Alkylene interrupted by O, S, SO, SO_2 or N-R_5 (representing bivalent radical A) preferably represents butylene or pentylene interrupted by O, S, SO, SO_2 or N-R_5.

A lower alkoxy (or alkyloxy) group preferably contains 1-4 carbon atoms, and represents for example methoxy, ethoxy, propoxy, isopropoxy, butoxy or isobutoxy.

Halogen (or halo) preferably represents chloro or fluoro but may also be bromo or iodo.

Aryl represents carbocyclic or heterocyclic aryl.

Carbocyclic aryl represents monocyclic or bicyclic aryl, for example phenyl or phenyl mono-, di- or tri-substituted by one, two or three radicals selected from lower alkyl, lower alkoxy, hydroxy, halogen, amino, mono-or di-lower alkylamino, cyano, carboxyl, esterified carboxyl, amidated carboxyl, trifluoromethyl, trifluoromethoxymethyl, lower alkylenedioxy, lower alkyl-(thio, sulfinyl or sulfonyl) and oxy-C_2-C_3-alkylene; or 1- or 2-naphthyl. Lower alkylenedioxy is a divalent substituent attached to two adjacent carbon atoms of phenyl, e.g. methylenedioxy or ethylenedioxy. Oxy-C_2-C_3-alkylene is also a divalent substituent attached to two adjacent carbon atoms of phenyl, e.g. oxyethylene or oxypropylene. An example for oxy-C_2-C_3-alkylene-phenyl is 2,3-dihydrobenzofuran-5-yl.

Preferred as carbocyclic aryl is phenyl or phenyl monosubstituted by lower alkoxy, halogen, lower alkyl or trifluoromethyl, especially phenyl or phenyl monosubstituted by lower alkoxy, halogen or trifluoromethyl, and in particular phenyl.

Heterocyclic aryl represents monocyclic or bicyclic heteroaryl, for example pyridyl, quinolinyl, isoquinolinyl, benzothienyl, benzofuranyl, benzopyranyl, benzothiopyranyl, furanyl, pyrrolyl, thiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, imidazolyl, thienyl, or any said radical substituted, especially mono- or di-substituted, by e.g. lower alkyl or halogen. Pyridyl represents 2-, 3- or 4-pyridyl, advantageously 3- or 4-pyridyl. Thienyl represents 2- or 3-thienyl, advantageously 2-thienyl. Quinolinyl represents preferably 2-, 3- or 4-quinolinyl, advantageously 2-quinolinyl. Isoquinolinyl represents preferably 1-, 3- or 4-isoquinolinyl. Benzopyranyl, benzothiopyranyl represent preferably 3-benzopyranyl or 3-benzothiopyranyl, respectively. Thiazolyl represents preferably 2- or 4-thiazolyl, advantageously 4-thiazolyl. Triazolyl is preferably 1-, 2- or 5-(1,2,4-triazolyl). Tetrazolyl is preferably 5-tetrazolyl. Imidazolyl is preferably 4-imidazolyl.

Preferably, heterocyclic aryl is pyridyl, quinolinyl, pyrrolyl, thiazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, imidazolyl, thienyl, or any said radical substituted, especially mono- or di-substituted, by lower alkyl or halogen; and in particular pyridyl.

Biaryl is preferably carbocyclic biaryl, e.g. biphenyl, namely 2-, 3- or 4-biphenyl, advantageously 4-biphenyl, each optionally substituted by e.g. lower alkyl, lower alkoxy, halogen, trifluoromethyl or cyano.

Cycloalkyl represents a saturated cyclic hydrocarbon optionally substituted by lower alkyl which contains 3 to 10 ring carbons and is advantageously cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl optionally substituted by lower alkyl.

Bicycloalkyl represents bornyl, norbornyl and the like.

Carbocyclic aryl-lower alkyl represents preferably straight chain or branched aryl-C_1-C_4-alkyl in which carbocyclic aryl has meaning as defined above, e.g. benzyl or phenyl-(ethyl, propyl or butyl), each unsubstituted or substituted on phenyl ring as defined under carbocyclic aryl above, advantageously optionally substituted benzyl.

Heterocyclic aryl-lower alkyl represents preferably straight chain or branched heterocyclic aryl-C_1-C_4-alkyl in which heterocyclic aryl has meaning as defined above, e.g. 2-, 3- or 4-pyridylmethyl or (2-, 3- or 4-pyridyl)-(ethyl, propyl or butyl); or 2- or 3-thienylmethyl or (2- or 3-thienyl)-(ethyl, propyl or butyl); 2-, 3- or 4-quinolinylmethyl or (2-, 3- or 4-quinolinyl)-(ethyl, propyl or butyl); or 2- or 4-thiazolylmethyl or (2- or 4-thiazolyl)-(ethyl, propyl or butyl).

Cycloalkyl-lower alkyl represents e.g. (cyclopentyl- or cyclohexyl)-(methyl or ethyl).

Acyl is derived from an organic carboxylic acid, carbonic acid or carbamic acid.

Acyl represents e.g. lower alkanoyl, carbocyclic aryl-lower alkanoyl, lower alkoxycarbonyl, lower alkoxy-lower alkanoyl, aroyl, di-lower alkylaminocarbonyl, di-lower alkylamino-lower alkanoyl, (piperidino, morpholino, or pyrrolidino)-carbonyl or (piperidino, morpholino, or pyrrolidino)-lower alkanoyl. Preferably, acyl is lower alkanoyl.

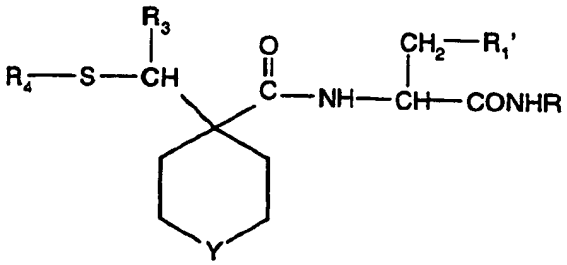
Lower alkanoyl represents e.g. C_1-C_7-alkanoyl including formyl, and is preferably C_2-C_4-alkanoyl such as acetyl or propionyl.

Aroyl represents e.g. benzoyl or benzoyl mono- or di-substituted by one or two radicals selected from lower alkyl, lower alkoxy, halogen, cyano and trifluoromethyl; or 1- or 2-naphthoyl; and also heterocyclic aroyl, e.g. pyridylcarbonyl.

Lower alkoxycarbonyl represents preferably C_1-C_4-alkoxycarbonyl, e.g. ethoxycarbonyl.

Preferred embodiments of the invention relate to the compounds of formula I wherein the A-containing ring is a cyclopropane, cyclopentane, cyclohexane, tetrahydropyran, tetrahydrofuran, pyrrolidine or piperidine ring.

A particular embodiment of the invention relates to the compounds of formula II



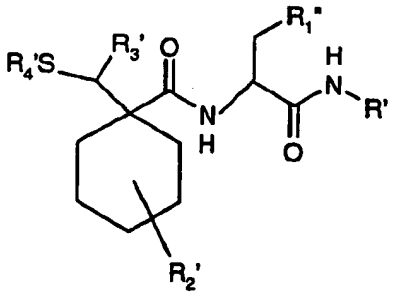
(II)

wherein R, R_3, R_4 and R_5 have meaning as defined above,

R_1' represents cycloalkyl, aryl or biaryl; and

Y represents CHR_2, S, SO, SO_2, O, or NR_5.

A further embodiment relates to the compounds of formula III

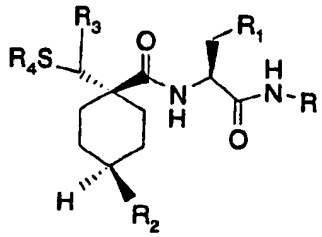


(III)

wherein R' is carbocyclic or heterocyclic aryl, carbocyclic or heterocyclic aryl-lower alkyl, cycloalkyl or lower alkyl; R_1" is carbocyclic or heterocyclic aryl, or biaryl; R_2' is hydrogen, lower alkyl or lower alkoxy; R_3' is hydrogen, lower alkyl or carbocyclic aryl-lower alkyl; and R_4' is hydrogen, lower alkanoyl, aryl-lower alkanoyl or aroyl.

Preferred are said compound of formula III wherein R_2 is at the 4-position of the cyclohexane ring.

Further preferred are compounds of formula IV



(IV)

wherein, R_2 and the amide chain are cis to each other, and R, R_1, R_2, R_3 and R_4 have meaning as defined hereinabove.

Preferred in turn are said compounds of formula IV wherein R is monocyclic carbocyclic or heterocyclic aryl; R_1 is monocyclic carbocyclic aryl; R_2 is lower alkoxy; R_3 is hydrogen; and R_4 is hydrogen or lower alkanoyl.

The compounds of the invention exhibit valuable pharmacological properties in mammals including man.

The compounds of the invention inhibit matrix degrading metalloproteinase such as gelatinase, stromelysin, collagenase (including collagenase 1 and 3), and macrophage metalloelastase, and membrane type matrix metalloproteinases, such as MT-MMP 1 and 2. They are particularly useful as collagenase-3 inhibitors. Compounds of the invention are also inhibitors of TNF-alpha converting enzyme (TNF-alpha convertase) and thus inhibit TNF alpha activity, e.g. suppress the production and/or release of TNF alpha, an important mediator of inflammation and tissue growth.

Thus the compounds of the invention inhibit matrix degradation and are useful for the treatment of gelatinase-, stromelysin-, collagenase-, TNF alpha-, MT-MMP-1 and 2- and

macrophage metalloelastase-dependent pathological conditions in mammals. Such conditions include malignant and non-malignant tumors (by inhibiting tumor growth, tumor metastasis, tumor progression or invasion and/or tumor angiogenesis), such tumors including e.g. breast, lung, bladder, colon, ovarian, and skin cancer. Other conditions to be treated with the compounds of the invention include rheumatoid arthritis osteoarthritis, bronchial disorders (such as asthma by inhibiting the degradation of elastin), atherosclerotic conditions (by e.g. inhibiting rupture of atherosclerotic plaques), as well as acute coronary syndrome, heart attacks (cardiac ischemia), strokes (cerebral ischemias), restenosis after angioplasty, and also vascular ulcerations, ectasia and aneurysms.

Further conditions to be treated with the compounds of the invention are inflammatory demyelinating disorders of the nervous system in which myelin destruction or loss is involved (such as multiple sclerosis), optic neuritis, neuromyelitis optica (Devic's disease), diffuse and transitional sclerosis (Schilder's disease) and acute disseminated encephalomyelitis, also demyelinating peripheral neuropathies such as Landry-Guillain-Barre-Strohl syndrome for motor defects; also tissue ulceration (e.g. epidermal and gastric ulceration), abnormal wound healing, periodental disease, bone disease (e.g. Paget's disease and osteoporosis). Also endometriosis, septic shock, inflammatory bowel disease, Crohn's disease and the like.

Ocular applications of the compounds of the invention include the treatment of ocular inflammation, corneal ulcerations, pterygium, keratitis, keratoconus, open angle glaucoma, retinopathies, and also their use in conjunction with refractive surgery (laser or incisional) to minimize adverse effects.

The compounds are particularly useful for the treatment of e.g. inflammatory conditions, osteoarthritis, rheumatoid arthritis and tumors.

Beneficial effects are evaluated in pharmacological tests generally known in the art, including the tests assays and procedures, e.g. the in vitro and in vivo tests, as described or referenced in WO 97/22587.

Collagenase-3 inhibitory activity is determined as follows:
One nM stock solutions of substrate (MCA-Pro-Leu-Gly-Dpa-Ala-Arg-NH_2, J. Biol. Chem. 271, 1544-1550, 1996) and 10 nM stock solution of inhibitor are prepared in DMSO. They are diluted with assay buffer (20 nM tris at pH 7.5 containing 10 mM $CaCl_2$, 0.002% sodium azide) as needed. Recombinant pro-collagenase-3 is activated with 1 mM APMA, and stored in the assay buffer after extensive dialysis in the assay buffer. Recombinant enzyme solution (0.05 ml, 1.3 nM) is mixed with 0.05 mL of inhibitor solution at various concentrations for 10 minutes at room temperature. Then 0.025 mL of 8 µM substrate solution is added and fluorescence
(λ ex = 325; λ em = 405) is continuously measured at room temperature. The percent inhibition of collagenase-3 activity is determined from the effect of inhibitor at various concentrations on the change in fluorescence; the IC_{50} is determined graphically.

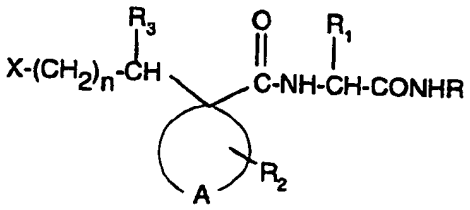
The effect on vascular aneurysms, e.g. the inhibition of aneurysm formation, can be determined in experimental models such as Apo-E transgenic mice and/or LDL receptor knockout mice.

Compounds on Formula I exhibit desirable properties in vitro and in vivo tests. For example compounds of Formula I have IC_{50}s of about 10 nM to about 5 µM, in particular from about 10 nM to about 500 nM, when tested to determine the inhibition of stromelysin activity according to the modified procedure of Harrison et al (Harrison, R.A., Teahan J., and Stein R., A semicontinuous, high performance chromatography based assay for stromelysin, Anal. Biochem. 180, 110-113 (1989)); have IC_{50}s of about 50 nm to about 5 µM, in particular from about 50 nM to about 500 nM, when tested in n assay for collagenase-1 activity and have IC_{50}s of about 5 to about 100 nM when tested in the above collagenase-3 inhibitory activity assay.

The compounds of the invention are particularly useful in mammals as antiinflammatory agents for the treatment of e.g. osteoarthritis, rheumatoid arthritis, and as antitumor agents for the treatment and prevention of tumors growth, tumor metastasis, tumor invasion or progression

and as antiatherosclerotic agents for the treatment and prevention of the rupture of atherosclerotic plaques.

The compounds of the invention, can be prepared by condensing under basic conditions a reactive intermediate of the formula V

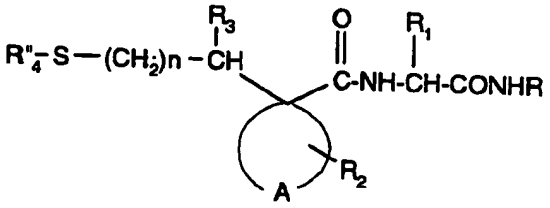


(V)

wherein R, R_1, R_2, R_3, n and A have meaning as previously defined, X represents a leaving group, e.g. a reactive esterified hydroxy group (such as bromo or (aryl- or alkyl)- sulfonyloxy) with a compound of the formula VI

$$R_4'' - SH \quad (VI)$$

or a metal salt thereof, wherein R_4'' represents an S-protecting group, e.g. acyl, t-butyl or optionally substituted benzyl; and further converting a resulting product of formula VII



(VII)

wherein R_4'' is t-butyl or optionally substituted benzyl to a corresponding compound of formula I wherein R_4 is hydrogen;

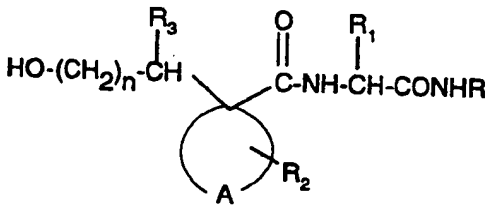
and, if necessary, temporarily protecting any interfering reactive group(s), and then liberating the resulting compound of the invention; and, if required or desired, converting a resulting compound of the invention into another compound of the invention, and/or, if desired, converting a resulting free compound into a salt or a resulting salt into a free compound or into

another salt; and/or separating a mixture of isomers or racemates obtained into the single isomers or racemates; and/or, if desired, resolving a racemate into the optical antipodes.

A reactive esterified hydroxy group in a compound of formula V represents hydroxy esterified by a strong acid, especially a strong inorganic acid, such as a hydrohalic acid, especially hydrochloric, hydrobromic or hydroiodic acid, or by a strong organic acid, especially a strong organic sulfonic acid, such as an aliphatic or aromatic sulfonic acid, for example methanesulfonic acid, 4-methylbenzene sulfonic acid or 4-bromobenzenesulfonic acid. A said reactive esterified derivative is especially halogen, for example chloro, bromo or iodo, or aliphatically or aromatically substituted sulfonyloxy, for example methanesulfonyloxy, 4-methylbenzenesulfonyloxy (tosyloxy) or trifluoromethanesulfonyloxy.

The above process for the synthesis of compounds of the invention can be carried out according to reactions generally known in the art, using customary solvents, e.g. inert solvents and protecting groups as appropriate, e.g. as described in WO 97/22587.

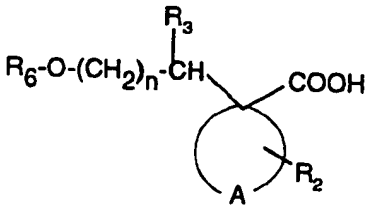
The starting materials of formula V can in turn be prepared from a corresponding compound of the formula VIII



(VIII)

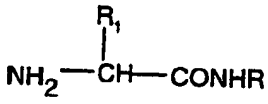
according to methods well-known in the art, e.g. by treatment with methanesulfonyl chloride in an inert solvent (such as methylene chloride) and in the presence of a base, such as triethylamine.

The intermediates of formula VIII can in turn be prepared by condensation of a compound of formula IX



(IX)

or a reactive functional derivative thereof wherein R_6 is an O-protecting group (such as benzyl) with a compound of the formula X



(X)

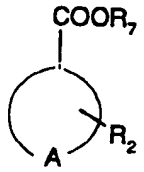
under conditions well known in the art for peptide synthesis.

The condensation with a free carboxylic acid of formula IX is carried out advantageously in the presence of a condensing agent such as dicyclohexylcarbodiimide or N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide in the presence of hydroxybenzotriazole, 1-hydroxy-7-azabenzotriazole, 1-hydroxy-, benzotriazole or benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP Reagent), and of triethylamine or N-methylmorpholine, in an inert polar solvent such as dimethylformamide or methylene chloride, preferably at room temperature.

Reactive functional derivatives of carboxylic acids of formula IX are preferably acid halides (e.g. the acid chloride) and mixed anhydrides, such as the pivaloyl or isobutyloxycarbonyl anhydride, or activated esters such as the benzotriazole, 7-azabenzotriazole or hexafluorophenyl ester.

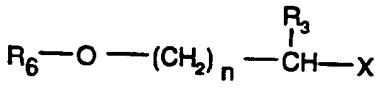
The condensation with a reactive functional derivative of an acid of formula IX in the form of an acid halide, advantageously an acid chloride, or mixed anhydride, is carried out in an inert solvent such as toluene or methylene chloride, advantageously in the presence of a base, e.g. an inorganic base such as potassium carbonate or an organic base such as triethylamine, N-methylmorpholine or pyridine, preferably at room temperature.

As to the synthesis of the intermediates of formula IX, such can be prepared by condensation of a compound of formula XI



(XI)

wherein $COOR_7$ represents esterified carboxyl, e.g. lower alkoxycarbonyl, with e.g. a compound of the formula XII



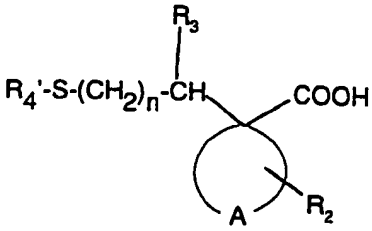
(XII)

wherein R_6 is an O-protecting group (such as benzyl) and X is reactive esterified hydroxyl, such as halo or alkylsulfonyloxy, in the presence of a strong anhydrous base, such as lithium diethylamide, in a solvent such as tetrahydrofuran.

The described condensation for the preparation of intermediates of formula IX (when R_2 is not hydrogen) which can lead to cis and trans isomers occurs in a stereoselective fashion. For example, the condensation of 4-R_2-substituted cyclohexanecarboxylic acid esters with e.g. benzyloxymethyl chloride leads predominantly to intermediates in which the R_2 and carboxyl groups are cis to each other. Such cis intermediates can then be converted to final products of formula IV (with stereochemistry as indicated) using an L-aminoacid amide in the subsequent condensation.

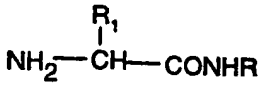
The starting materials of formula X, XI and XII are known in the art or can be prepared according to analogous methods known in the art.

Alternately, the compounds of formula I can be prepared by condensing a compound of the formula XIII



(XIII)

or a reactive functional derivative thereof wherein A, n, R_2 and R_3 have meaning as defined hereinabove and R_4' represents an S-protecting group, e.g. acyl, t-butyl or optionally substituted benzyl, with a compound of formula X

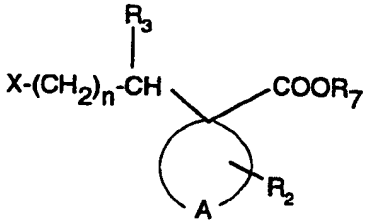


(X)

wherein R and R_1 have meaning as defined above.

This method is advantageously used for compounds wherein R_3 is other than hydrogen.

The intermediates of formula XIII can in turn be prepared by treating a compound of the formula



(XIV)

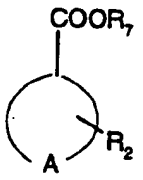
wherein A, X, n, R_2 and R_3 have meaning as defined hereinabove and $COOR_7$ represents esterified carboxyl, e.g. lower alkoxycarbonyl with a compound of formula VI

$$R_4\text{" - SH} \quad \text{(VI)}$$

or a metal salt thereof wherein R_4" has meaning as defined herein above.

The alcohol precursors to the starting materials of formula XIV can be obtained by essentially using methodology described above for the synthesis of intermediates of formula IX, and deprotecting the corresponding O - R_6 protected intermediates.

The alcohol precursors to the intermediates of formula XIII wherein n is zero can be advantageously prepared by condensing a compound of formula XI

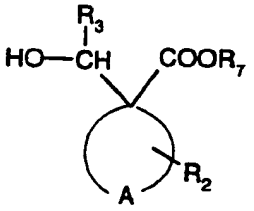


(XI)

wherein $COOR_7$ is esterified carboxyl with an aldehyde of the formula XV

$$R_3 - CHO \quad (XV)$$

under anhydrous basic conditions, e.g. in the presence of lithium diethylamide, to yield a compound of formula XVI



(XVI)

which can in turn be converted to the corresponding reactive intermediate of formula XIV wherein n is zero.

The above-mentioned reactions are carried out according to standard methods. The preferred solvents, catalysts and reaction conditions are set forth in the appended illustrative examples.

The invention further includes any variant of the present processes, in which an intermediate product obtainable at any stage thereof is used as starting material and the remaining steps are carried out, or in which the starting materials are formed in situ under the reaction conditions,

or in which the reaction components are used in the form of their salts or optically pure antipodes.

Compounds of the invention and intermediates can also be converted into each other according to methods generally known per se.

The free mercaptans may be converted to the S-acyl derivatives by reaction with a reactive derivative of a carboxylic acid (corresponding to the acyl group R_4 in formula I), such as an acid anhydride or acid chloride, preferably in the presence of cobalt chloride ($CoCl_2$) in an inert solvent such as acetonitrile or methylene chloride.

The free mercaptans, wherein R_4 represents hydrogen, may be oxidized to the corresponding disulfides, e.g. by air oxidation or with the use of mild oxidizing agents such as iodine in alcoholic solution. Conversely, disulfides may be reduced to the corresponding mercaptans, e.g. with reducing agents such as sodium borohydride, zinc and acetic acid or tributylphosphine.

Carboxylic acid esters may be prepared from a carboxylic acid by condensation with e.g. the halide corresponding to R_2-OH, in the presence of a base, or with an excess of the alcohol in the presence of an acid catalyst, according to methods well-known in the art.

Carboxylic acid esters and S-acyl derivatives may be hydrolyzed, e.g. with aqueous alkali such as alkali metal carbonates or hydroxides.

The invention also relates to any novel starting materials and processes for their manufacture.

Depending on the choice of starting materials and methods, the new compounds may be in the form of one of the possible isomers or mixtures thereof, for example, as substantially pure geometric (cis or trans) isomers, optical isomers (antipodes), racemates, or mixtures thereof. The aforesaid possible isomers or mixtures thereof are within the purview of this invention.

Any resulting mixtures of isomers can be separated on the basis of the physico-chemical differences of the constituents, into the pure geometric or optical isomers, diastereoisomers, racemates, for example by chromatography and/or fractional crystallization.

Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by known methods, e.g. by separation of the diastereoisomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. The carboxylic acid intermediates can thus be resolved into their optical antipodes e.g. by fractional crystallization of d- or l-(alpha-methylbenzylamine, cinchonidine, cinchonine, quinine, quinidine, ephedrine, dehydroabietylamine, brucine or strychnine)-salts. Racemic products can also be resolved by chiral chromatography, e.g. high pressure liquid chromatography using a chiral adsorbent.

Finally, compounds of the invention are either obtained in the free form, or as a salt thereof if salt forming groups are present.

Acidic compounds of the invention may be converted into salts with pharmaceutically acceptable bases, e.g. an aqueous alkali metal hydroxide, advantageously in the presence of an ethereal or alcoholic solvent, such as a lower alkanol. From the solutions of the latter, the salts may be precipitated with ethers, e.g. diethyl ether. Resulting salts may be converted into the free compounds by treatment with acids. These or other salts can also be used for purification of the compounds obtained.

Compounds of the invention having basic groups can be converted into acid addition salts, especially pharmaceutically acceptable salts. These are formed, for example, with inorganic acids, such as mineral acids, for example sulfuric acid, a phosphoric or hydrohalic acid, or with organic carboxylic acids, such as (C_1-C_4)-alkanecarboxylic acids which, for example, are unsubstituted or substituted by halogen, for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, succinic, maleic or fumaric acid, such as hydroxycarboxylic acids, for example glycolic, lactic, malic, tartaric or citric acid, such as

amino acids, for example aspartic or glutamic acid, or with organic sulfonic acids, such as (C_1-C_4)-alkylsulfonic acids (for example methanesulfonic acid) or arylsulfonic acids which are unsubstituted or substituted (for example by halogen). Preferred are salts formed with hydrochloric acid, methanesulfonic acid and maleic acid.

In view of the close relationship between the free compounds and the compounds in the form of their salts, whenever a compound is referred to in this context, a corresponding salt is also intended, provided such is possible or appropriate under the circumstances.

The compounds, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization.

The pharmaceutical compositions according to the invention are those suitable for enteral, such as oral or rectal, transdermal, topical and parenteral administration to mammals, including man, to inhibit TNF-alpha converting enzyme and matrix-degrading metalloproteinases, and for the treatment of disorders responsive thereto, comprising an effective amount of a pharmacologically active compound of the invention, alone or in combination, with one or more pharmaceutically acceptable carriers.

For example, the invention includes pharmaceutical compositions, formulations, combination with other therapeutic agents, dosages, dosage forms and methods of use as described in WO 97/22587. The relevant teachings of WO 97/22587, for instance as referred to above are incorporated within the teaching of the present application.

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees Centrigrade. If not mentioned otherwise, all evaporations are performed under reduced pressure, preferably between about 15 and 100mm Hg (= 20-133 mbar). The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, e.g. microanalysis and spectroscopic characteristics (e.g. MS, IR, NMR). Abbreviations used are those conventional in the art. The concentration for $[a]_D$ determinations is expressed in mg/ml.

Example 1

(a) To a solution of 2-[N-(1-methanesulfonyloxymethyl-4-methoxycyclohexanecarbonyl)-amino]-3-phenylpropionic acid N-phenylamide (1.63 g, 2.68 mmol) in acetonitrile (50 mL) is added potassium thioacetate (0.61 g, 5.36 mmol) The mixture is heated to reflux for 15 hours and then cooled. The organic phase is washed with brine, decolorized, and the solvent is removed to yield an oil. The oil is purified by flash chromatography (SiO_2, hexane/ethyl acetate, 1% methanol) to give (S)-2-[N-(1-(acetylmercaptomethyl)-cis-4-methoxycyclohexane-carbonyl)amino]-3-phenylpropionic acid N-phenylamide as a solid. ^1H NMR ($CDCl_3$) d 7.75 (s, 1H), 7.32 (m, 9H), 7.10 (t, 1H), 6.45 (d, 1H), 4.75 (q, 1H), 3.30 (s, 3H), 3.16 (m, 3H), 3.08 (s, 2H), 2.22 (s, 3H), 2.12-1.80 (m, 4H), 1.30 (m, 4H). This is the compound of Formula IV wherein R is phenyl, R_1' is phenyl, R_2 is methoxy, R_3 is H and R_4 is acetyl.

The starting materials are prepared as follows:

To a stirred solution of N-BOC-L-phenylalanine (20 g, 75.4 mmol) in methylene chloride (200 mL) is added aniline (7.0 mL, 75.4 mmol), dicyclohexylcarbodiimide (15.5 g, 75.4 mmol), and 1-hydroxy-7-azabenzotriazole (10.3 g, 75.4 mmol). The mixture is stirred at room temperature overnight. The solid is filtered away and the filtrate is washed with 5% citric acid (50 mL), a saturated solution of sodium bicarbonate (50 mL), and brine (50 mL). The organic phase is dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield a light brown solid. The solid is recrystalized from ethyl acetate to afford N-BOC-L-phenylalanine-N-phenylamide as a white solid (11 g).

To a solution of N-BOC-L-phenylalanine-N-phenylamide (1.7 g, 5 mmol) in methylene chloride (75 mL) is bubbled dry HCl gas for 15 minutes. The solvent is then removed under reduced pressure to give a white foam, mp 215-216°C. ^1H NMR (DMSO-d_6) d 10.9 (s, 1H), 8.5 (bs, 3H), 7.4-7.1 (m, 10H), 4.3 (t, 1H), 3.15 (m, 2H).

To a solution of diisopropylamine (7.27 g, 72 mmol) in tetrahydrofuran (100 mL) at -50°C is added 2.5 M n-butyl lithium (28.8 mL, 72 mmol). The mixture is warmed to 0°C and stirred for 10 minutes. The solution is cooled to -50°C and 4-methoxycyclohexylcarboxylic acid methyl ester (10.33 g, 60 mmol) is added dropwise. The mixture is allowed to slowly warm to 0°C and is stirred for 30 minutes. The mixture is again cooled to 0°C and then benzyl chloromethyl ether (11.3 g, 72 mmol) is added dropwise. The mixture is allowed to warm to room temperature and is stirred overnight. The solvent is then removed in vacuo and hexane is added to the residue. The organic phase is washed with 1N HCl, a saturated solution of sodium bicarbonate, and brine. The organic phase is dried over magnesium sulfate, filtered and the solvent is removed in vacuo to give an oil. The oil is dissolved in ethanol (70 mL) and water (70 mL) and potassium hydroxide (6.84 g, 120 mmol) is added. The mixture is heated to reflux for 16 hours and then concentrated in vacuo. A 1N solution of sodium hydroxide is added and the aqueous phase is washed with ether and then acidified with concentrated HCl. The aqueous phase is extracted with ethyl acetate, dried over magnesium sulfate, filtered, and the solvent is removed to give a solid. The solid is washed with hexane and dried at 50°C to afford cis-1-benzyloxymethyl-4-methoxycyclohexanecarboxylic acid as a white solid.

To a solution of cis-1-benzyloxymethyl-4-methoxycyclohexanecarboxylic acid (1.39 g, 5 mmol) in methylene chloride (50 mL) is added L-phenylalanine-N-phenylamide (1.38 g, 5 mmol), triethylamine (0.51 g, 5 mmol), 1-hydroxy-7-azabenzotriazole (0.82 g, 6 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide(1.15 g, 6 mmol). The mixture is stirred at room temperature overnight and then the organic phase is washed with a saturated solution of sodium bicarbonate, 5% citric acid, and brine. The solution is dried over magnesium sulfate, filtered and concentrated *in vacuo* to give (S)-2-[N-(1-benzyloxymethyl-cis-4-methoxy-cyclohexanecarbonyl)amino]-3-phenylpropionic acid N-phenylamide as an oil.

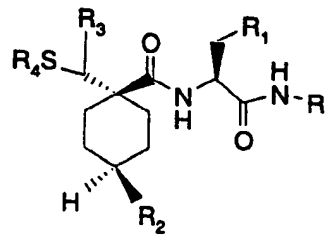
A solution of (S)-2-[N-(1-benzyloxymethyl-cis-4-methoxycyclohexanecarbonyl)amino]-3-phenylpropionic acid N-phenylamide (2.40 g, 4.8 mmol) in ethanol (75 mL) and concentrated HCl (0.5 mL) with 10% Pd/C (0.24 g) is hydrogenated on a Parr hydrogenation

apparatus for 90 minutes at 60 psi. The catalyst is removed by filtration and concentrated in vacuo to give

2-[N-(1-hydroxymethyl-4-methoxycyclohexanecarbonyl)amino]-3-phenylpropionic acid N-phenylamide as an oil. ^{1}H NMR ($CDCl_3$) d 8.35 (s, 1H), 7.25 (m, 10H), 7.06 (t, 1H), 4.3 (t, 1H), 6.48 (d, 1H), 4.88 (q, 1H), 3.46 (dq, 2H), 3.29 (s, 3H), 3.16 (d, 2H), 3.02 (m, 1H), 2.08 (m, 2H), 1.87 (m, 2H), 1.22 (m, 4H).

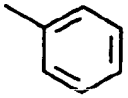
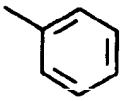
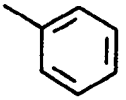
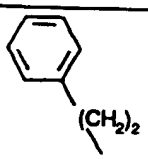
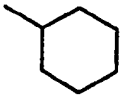
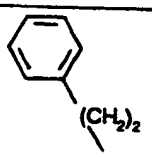
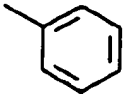
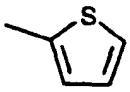
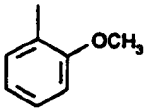
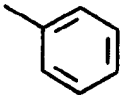
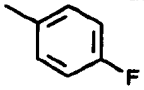
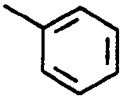
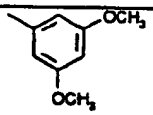
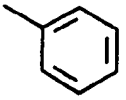
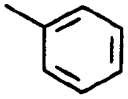
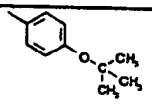
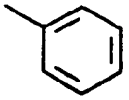
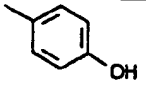
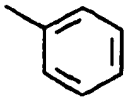
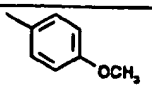
To a solution of (S)-2-[N-(1-hydroxymethyl-cis-4-methoxycyclohexanecarbonyl)amino]-3-phenylpropionic acid N-phenylamide (1.1 g, 2.68 mmol) in methylene chloride (50 mL) is added triethylamine (1.78 mL, 13.4 mmol) and mesyl chloride (1.53 g, 13.4 mmol). The mixture is stirred at room temperature for 1 hour and then the organic phase is removed. The residue is dissolved in methylene chloride (100 mL) and washed with a saturated solution of sodium bicarbonate, 5% citric acid, brine, and then dried over magnesium sulfate. The solution is filtered and concentrated to give an oil which is purified by flash chromatography (SiO_2, : 2.5: 0.5, hexane: ethyl acetate: methanol). (S)-2-[N-(1-Methanesulfonyloxymethyl-cis-4-methoxycyclohexanecarbonyl)amino]-3-phenylpropionic acid N-phenylamide is obtained as a clear oil.

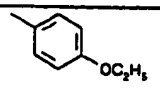
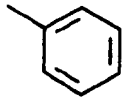
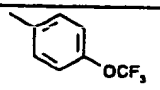
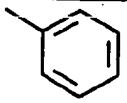
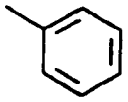
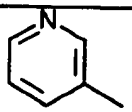
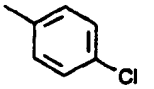
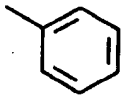
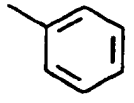
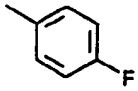
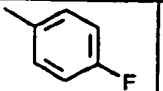
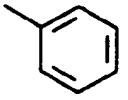
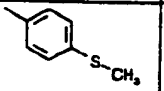
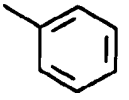
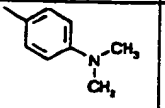
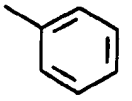
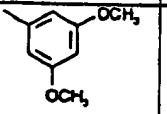
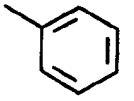
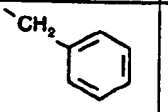
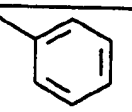
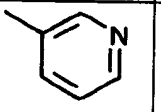
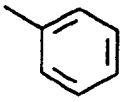
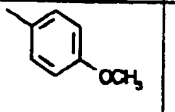
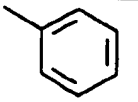
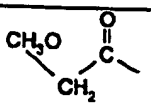
By repeating the procedures described above in Example 1 using appropriate starting materials the following compounds of Formula IV' are similarly prepared.

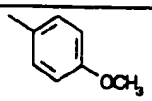
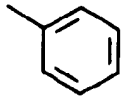
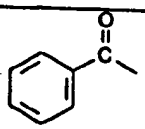
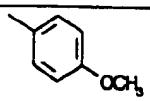
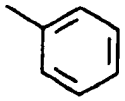
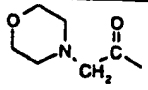
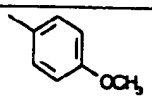
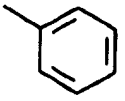
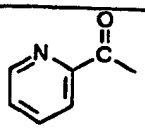
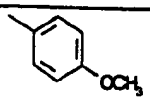
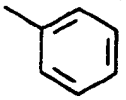
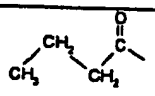
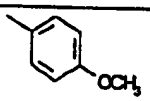
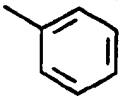
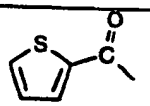
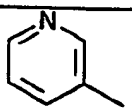
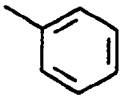
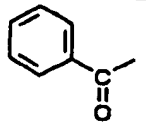
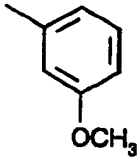
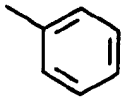


IV'

TABLE 1

Example No.	R	R_1	R_2	R_3	R_4	mp °C
2			C_2H_5O-	H	CH_3CO-	145-146
3	CH_3-		H		CH_3CO-	60-64
4	CH_3-		CH_3O-		CH_3CO-	160-161
5	CH_3-	$(CH_3)_2CH$-	CH_3O-	H	CH_3CO-	138-139
6			C_2H_5O-	H	CH_3CO-	148-150
7			C_2H_5O-	H	CH_3CO-	128-129
8			C_2H_5O-	H	CH_3CO-	142-143
9			C_2H_5O-	H	CH_3CO-	148-149
10			C_2H_5O-	H	CH_3CO-	130-132
11			C_2H_5O-	H	CH_3CO-	77-78
13			C_2H_5O-	H	CH_3CO-	139-141

Example No.	R	R_1	R_2	R_3	R_4	mp °C
14			C_2H_5O-	H	CH_3CO-	155-156
15			C_2H_5O-	H	CH_3CO-	138-139
16			C_2H_5O-	H	CH_3CO-	135-137
17			C_2H_5O-	H	CH_3CO-	177-178
18			C_2H_5O-	H	CH_3CO-	127-129
19			C_2H_5O-	H	CH_3CO-	160-163
20			C_2H_5O-	H	CH_3CO-	146-147
21			C_2H_5O-	H	CH_3CO-	127
22			CH_3O-	H	CH_3CO-	162-163
23			CH_3O-	H	CH_3CO-	149-150
24			CH_3O-	H	CH_3CO-	143-144
25			CH_3O-	H		138-139

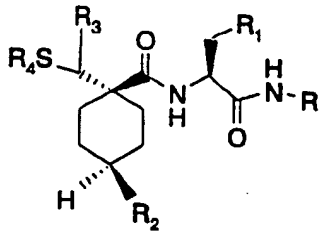
Example No.	R	R_1	R_2	R_3	R_4	mp °C
26			C_2H_5O-	H		165-166
27			C_2H_5O-	H		172-173
28			C_2H_5O-	H		87-88
29			C_2H_5O-	H		144-145
30			C_2H_5O-	H		foam
31			C_2H_5O-	H		75-80
32			C_2H_5O-	H	CH_3CO-	132-133

Example 33

(a) To a stirred degassed solution of (S)-2-[N-(1-acetylmercaptomethyl-cis-4-methoxy-cyclohexanecarbonyl)amino]-3-phenylpropionic acid N-phenylamide (0.60 g, 1.28 mmol) in methanol (30 mL) under nitrogen at room temperature is added degassed 1N NaOH (2.50 mL, 2.56 mmol). The solution is stirred for 1 hour and then acidified to pH 1 with 1N HCl. The

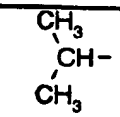
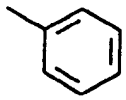
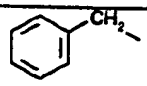
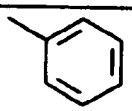
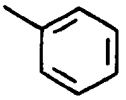
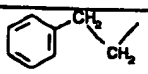
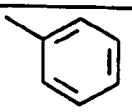
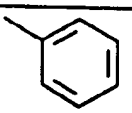
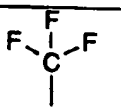
methanol is removed in vacuo to yield a suspension of a yellow solid in water. The solid is collected by filtration, washed with water and dried in vacuo at 50°C for 16 hours to give (S)-2-[N-(1-mercaptomethyl-cis-4-methoxycyclohexanecarbonyl)amino]-3-phenylpropionic acid N-phenylamide, mp 171-172°C. ^{1}H NMR ($CDCl_3$) d 7.94 (s, 1H), 7.30 (m, 9H), 7.09 (t, 1H), 6.43 (d, 1H), 4.95 (q, 1H), 3.30 (s, 3H), 3.23 (dd, 2H), 3.16 (m, 2H), 2.67 (m, 2H), 2.13 (m, 2H), 1.82 (m, 2H), 1.33 (m, 4H). Anal cald. C, 67.58; H, 7.09; N, 6.57, found C, 67.39; H, 7.08; N, 6.48. This is the compound of formula IV wherein R is phenyl, R_1' is phenyl, R_2 is methoxy and R_3 and R_4 are hydrogen.

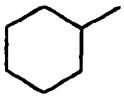
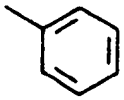
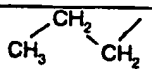
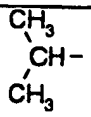
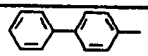
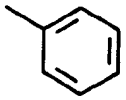
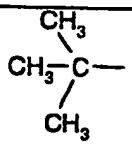
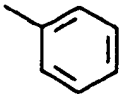
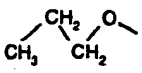
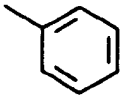
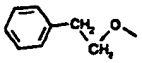
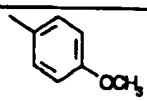
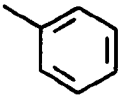
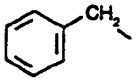
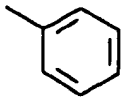
By repeating the procedures described above in Example 33 using appropriate starting materials the following compounds of Formula IV' are similarly prepared.

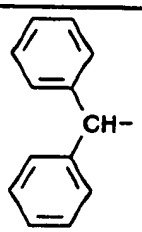
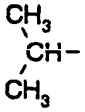
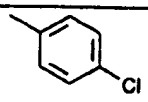
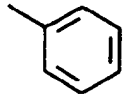
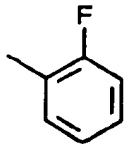
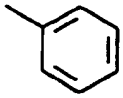
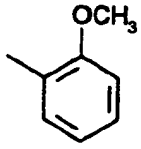
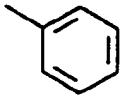
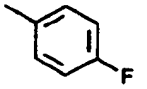
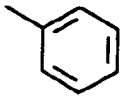
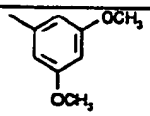
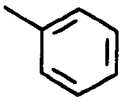
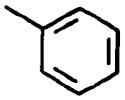
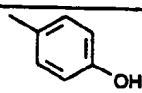
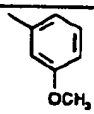
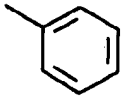
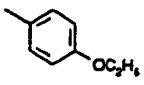
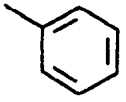


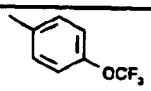
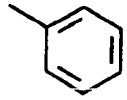
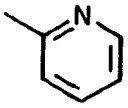
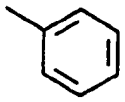
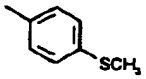
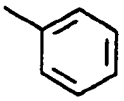
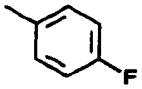
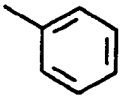
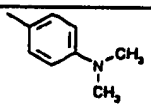
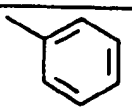
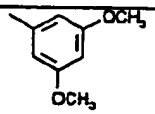
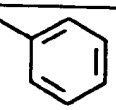
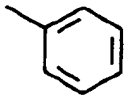
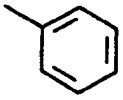
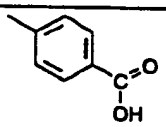
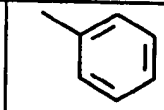
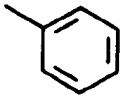
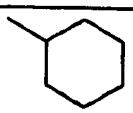
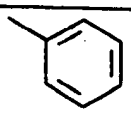
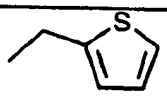
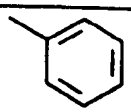
IV'

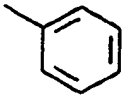
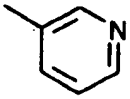
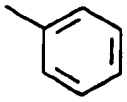
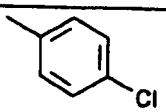
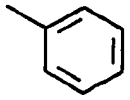
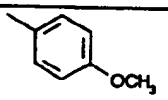
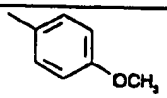
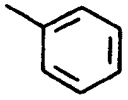
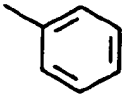
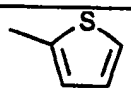
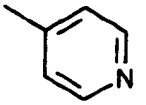
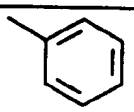
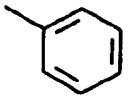
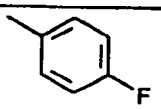
TABLE 2

Example No.	R	R_1	R_2	R_3	R_4	mp °C
34			C_2H_5O-	H	H	159-160
35			C_2H_5O-	H	H	91-92
36	CH_3-		H		H	61-65
37	CH_3-		C_2H_5O-	H	H	111-112
38	CH_3-			H	H	157.5-158.5

Example No.	R	R_1	R_2	R_3	R_4	mp °C
39	CH_3-		CH_3O-	H	H	161-162
40	CH_3-			H	H	136-137
41	CH_3-		CH_3O-	H	H	106-108
42	CH_3-		CH_3O-	H	H	135-136
43	CH_3-			H	H	122-124
44	CH_3-			H	H	50-52
45	CH_3-			H	H	49-52
46	CH_3-		CH_3O-	H	H	118-119
47	CH_3-		CH_3O-	H	H	125-126
48	CH_3-		H	H	H	165
49	CH_3-		H	H	H	85-88

Example No.	R	R_1	R_2	R_3	R_4	mp °C
50			CH_3O-	H	H	142-144
51			C_2H_5O-	H	H	175-176
52			C_2H_5O-	H	H	99-100
53			C_2H_5O-	H	H	97-98
54			C_2H_5O-	H	H	152-153
55			C_2H_5O-	H	H	166-167
56			C_2H_5O-	H	H	100-101
57			C_2H_5O-	H	H	114-115
58			C_2H_5O-	H	H	155-156

Example No.	R	R_1	R_2	R_3	R_4	mp °C
59			C_2H_5O-	H	H	179-180
60			C_2H_5O-	H	H	124-125
61			C_2H_5O-	H	H	189-190
62			CH_3O-	H	H	173-174
63			C_2H_5O-	H	H	162-163
64			CH_3O-	H	H	189-190
65			C_2H_5O-	H	H	163-164
66			C_2H_5O-	H	H	231-232
67			C_2H_5O-	H	H	189-190
68			C_2H_5O-	H	H	159-160
69			C_2H_5O-	H	H	137-138

Example No.	R	R_1	R_2	R_3	R_4	mp °C
70			C_2H_5O-	H	H	77-78
71			C_2H_5O-	H	H	180-181
72			C_2H_5O-	H	H	170-171
73			C_2H_5O-	H	H	151-152
74			C_2H_5O-	H	H	129-130
75			C_2H_5O-	H	H	133-137
76			C_2H_5O-	H	H	177-178

By repeating the procedures described above in Example 33 using appropriate starting materials the following compounds of Formula IV are similarly prepared.

Example 77: (S)-2-[N-(1-mercaptomethyl-cis-4-methoxycyclohexanecarbonyl)amino]-phenylacetic acid N- methylamide, mp 84-86°C;

Example 78: (S)-2-[N-(1-mercaptomethyl-3-methoxycyclohexanecarbonyl)amino]-3-phenylpropionic acid N-methylamide, oil.

Example 79: (S)-2-[N-(4-mercaptomethyl-1-acetylpiperidyl-4-carbonyl)-amino]-3-phenylpropionic acid N-methylamide, mp 76-78°C;

Example 80: (S)-2-[N-(4-mercaptomethyl-1-methylsulfonylpiperidyl-4-carbonyl)amino]-3-phenyl-propionic acid N-methylamide, mp 73-74°C;

Example 81: (S)-2-[N-(4-mercaptomethyl-1-benzylpiperidyl-4-carbonyl)amino]-3-phenylpropionic acid N-methylamide, mp 45°C.

Example 82: (S)-2-[N-1-(3-mercaptopropyl)-cis-4-methoxycyclohexanecarbonyl)amino]-3-phenyl-propionic acid N-methylamide, mp 101-102°C.

Example 83: (S)-2-[N-(1-mercaptomethyl)-cycloheptanecarbonyl)amino]-3-phenylpropionic acid N-methylamide, mp 128-129°C.

Example 84

Preparation of 3000 capsules each containing 25 mg of the active ingredient, for example 2-[N-(1-(acetylmercaptomethyl)-4-methoxycyclohexanecarbonyl)amino]-3-phenylpropionic acid N-phenylamide

Active ingredient	75.00 g
Lactose	750.00 g
Microcrystalline cellulose	300.00 g
Polyvinylpyrrolidone	30.00 g
Purified water	q.s.
Magnesium stearate	9.0

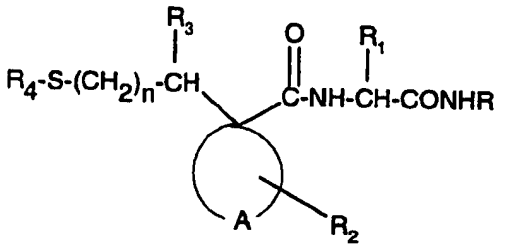
The active ingredient is passed through a No. 30 hand screen.

The active ingredient, lactose, cellulose and polyvinylpyrrolidone are blended for 15 minute in a mixer. The blend is granulated with sufficient water (about 500 mL), dried in an oven at 35°C overnight, and passed through a No. 20 screen.

Magnesium stearate is passed through a No. 20 screen, added to the granulation mixture, and the mixture is blended for 5 minutes in a mixer. The blend is encapsulated in No. 0 hard gelatin capsules each containing an amount of the blend equivalent of 10 mg of the active ingredient.

Claims:

1. A compound of the formula



(I)

wherein

R represents hydrogen, lower alkyl, cycloalkyl, bicycloalkyl, adamantyl, aryl, biaryl, or mono- or di-(cycloalkyl, aryl or biaryl)-lower alkyl, di-(lower alkyl or aryl-lower alkyl)amino-lower alkyl, or (piperidino, morpholino, pyrrolidino)-lower alkyl;

R_1 represents hydrogen, lower alkyl, cycloalkyl, aryl, biaryl, or (cycloalkyl, aryl or biaryl) - lower alkyl;

R_2 represents hydrogen, lower alkyl, lower alkoxy, aryl-lower alkyl, aryl-lower alkoxy, amino, mono- or di-(lower alkyl or aryl-lower alkyl)-amino, acylamino, or (lower alkyl or aryl-lower alkyl)-(thio, sulfinyl or sulfonyl);

R_3 represents hydrogen, lower alkyl, cycloalkyl, aryl-lower alkyl, cycloalkyl-lower alkyl, or C_2-C_7-alkyl interrupted by S, SO, SO_2, O or N-R_5;

R_4 represents hydrogen or acyl;

R_5 represents hydrogen, lower alkyl, aryl-lower alkyl, acyl, or (lower alkyl, aryl or aryl-lower alkyl)-sulfonyl;

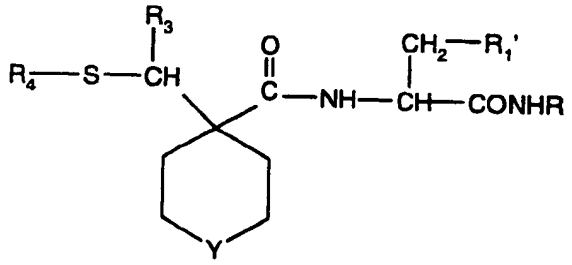
A together with the carbon to which it is attached forms a ring and represents a bivalent radical of the formula $(CH_2)_P$ which may be interrupted by S, SO, SO_2, O, or N-R_5;

n represents an integer from zero to four;

p represents an integer from 2 to 6;

or a pharmaceutically acceptable salt thereof; or a disulfide corresponding to said compound of formula I wherein R_4 is hydrogen.

2. A compound according to claim 1 of the formula



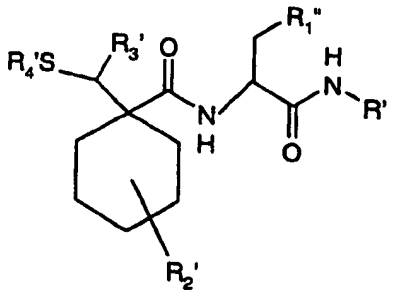
(II)

wherein R, R_3 and R_4 and R_5 have meaning as defined above,

R_1' represents cycloalkyl, aryl or biaryl; and

Y represents CHR_2, S, SO, SO_2, O, or NR_5.

3. A compound according to claim 1 of the formula III



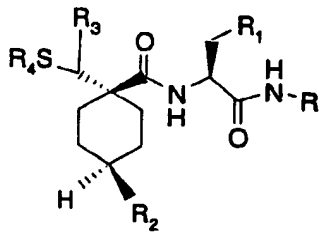
(III)

wherein R' is carbocyclic or heterocyclic aryl, carbocyclic or heterocyclic aryl-lower alkyl, cycloalkyl or lower alkyl; R_1" is carbocyclic or heterocyclic aryl, or biaryl; R_2' is hydrogen, lower alkyl or lower alkoxy; R_3' is hydrogen, lower alkyl or carbocyclic aryl-lower alkyl; and R_4' is hydrogen, lower alkanoyl, aryl-lower alkanoyl or aroyl.

4. A compound according to claim 2 wherein the configuration of the asymmetric carbon atom of the terminal amino acid amide moiety corresponds to that of an L-amino acid precursor and is assigned the (S)-configuration.

5. A compound according to claim 3 wherein R_2 is at the 4-position of the cyclohexane ring.

6. A compound according to claim 1 of the formula



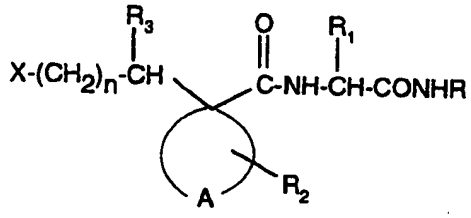
(IV)

wherein, R_2 and the amide chain are cis to each other, and R, R_1, R_2 and R_4 have meaning as defined in claim 1; and wherein the configuration of the asymmetric carbon atom of the terminal amino acid amide is assigned the (S)-configuration.

7. A compound according to claim 6 wherein R is monocyclic carbocyclic or heterocyclic aryl; R_1 is monocyclic carbocyclic aryl; R_2 is lower alkoxy; R_3 is hydrogen; and R_4 is hydrogen or lower alkanoyl.

8. A compound according to claim 1 selected from the group consisting of
2-[N-(1-mercaptomethyl-4-ethoxycyclohexanecarbonyl)amino]-3-phenylpropionic acid N-methylamide;
(S)-2-[N-(1-mercaptomethyl-cis-4-methoxycyclohexanecarbonyl)amino]-3-phenylpropionic acid N-phenylamide;
(S)-2-[N-(1-(1-mercapto-3-phenylpropyl)-cyclohexanecarbonyl)amino]-3-phenylpropionic acid N-methylamide, and
(S)-2-[N-(1-mercaptomethyl-cis-4-ethoxycyclohexanecarbonyl)amino]-3-phenylpropionic acid N-methylamide.

9. A process for the preparation of a compound of claim 1 which comprises condensing under basic conditions a reactive intermediate of the formula V



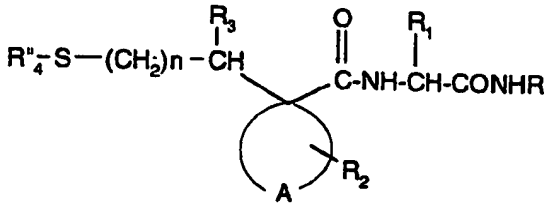
(V)

wherein R, R_1, R_2, R_3, n and A have meaning as previously defined, X represents a leaving group, e.g. a reactive esterified hydroxy group (such as bromo or (aryl - or alkyl) - sulfonyloxy)

with a compound of the formula VI

$$R_4'' - SH \quad (VI)$$

or a metal salt thereof, wherein R_4' represents an S-protecting group, e.g. acyl, t-butyl or optionally substituted benzyl;and further converting a resulting product of formula VII



(VII)

wherein R_4'' is t-butyl or optionally substituted benzyl to a corresponding compound of formula I wherein R_4 is hydrogen;

and, if necessary, temporarily protecting any interfering reactive group(s), and then liberating the resulting compound of the invention; and, if required or desired, converting a resulting compound of the invention into another compound of the invention, and/or, if desired, converting a resulting free compound into a salt or a resulting salt into a free compound or into another salt; and/or separating a mixture of isomers or racemates obtained into the single isomers or racemates; and/or, if desired, resolving a racemate into the optical antipodes.

INTERNATIONAL SEARCH REPORT

Ir. ational Application No
PCT/EP 98/01584

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C327/32 C07D333/24 C07D213/56 C07D295/14 C07D213/83
C07D333/38 C07C323/53 C07D213/75 C07D333/20 C07D333/36
C07D211/34 C07D211/96 A61K31/16 A61K31/625 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 91 09840 A (SCHERING CORPORATION) 11 July 1991 see claims 1-11,16-19	1,9
A	DATABASE CHEMABS CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US STN, accession no. 119:160823, XP002073604 see abstract; RN 149704-86-9 & JP 05 092 948 A (YOSHITOMI PHARMACEUTICAL) 16 April 1993	1
A	WO 95 12603 A (SYNTEX (USA) INC) 11 May 1995 see claims 1-7,15,16; examples 22,23	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 August 1998	17/08/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016	Van Amsterdam, L

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INTERNATIONAL SEARCH REPORT

In ational Application No
PCT/EP 98/01584

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/38

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

☐ Further documents are listed in the continuation of box C.

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 August 1998	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Amsterdam, L

2

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int .tional Application No
PCT/EP 98/01584

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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